Format for ANSWERING REVIEWERS

June 10, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript 3387-Review.docx).

Title: Diagnostic Accuracy of Cardiac Computed Tomography Angiography for Myocardial Infarction

Author: Monvadi B. Srichai, Hersh Chandarana, Robert Donnino, Irene Isabel P. Lim, Christianne Leidecker, James Babb, Jill E. Jacobs

Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 3387 (originally wjr-00289603)

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated in accordance to guidelines.

(1) The original title "Clinical Evaluation of Low, High and Mixed Voltage Cardiac Computed Tomography Angiography for Detection of Chronic Myocardial Infarction" has been changed and shortened to "Diagnostic Accuracy of Cardiac Computed Tomography Angiography for Myocardial Infarction" in response to reviewer 02468825 and in order to comply with journal format of 12 words or less.

(2) The structured abstract has been expanded to conform with the word limit guidelines for the AIM, METHODS, RESULTS and CONCLUSION.

(3) A Core Tip summary has been included after the Abstract and Key Words section.

(4) PMID and DOI numbers have been included for journal citations

2. In response to reviewer 00631937:

(1) Although in the results section, the authors mention that CCTA assigned territories were confirmed by one or more additional imaging studies (echocardiography [n=15], SPECT [n=5] or CMR [n=1]), the comparison to other commonly used techniques such as the ones mentioned is not fully discussed. It would be interesting to elaborate on how the DECT imaging compares to other imaging tools.

We agree that a comparison of CCTA with alternative techniques to identify prior MI would be interesting and provide additional clinical utility for this technique. However, given that at present there are many different CT technical algorithms for assessment of myocardial infarction, the intent of this study was to evaluate different late phase CT imaging techniques to identify the most reliable CCTA technique for identification of myocardial fibrosis. Although we did have corroborating data with regard to infarct location using other imaging techniques, again, as this was not the focus of this study, we did not have a significant number of a single other technique to allow for statistically valid comparisons. This study serves as a preliminary step for a clinical study to compare CCTA with other imaging techniques in the assessment of myocardial fibrosis from prior MI and/or other non-ischemic etiologies. We have included a paragraph in the Discussion section to discuss our limited findings with what is known in the literature regarding diagnostic accuracy of different imaging modalities for detection of myocardial infarction. The paragraph is as follows:

"Although we corroborated myocardial infarct location territories with other available studies, this study was not designed to be able to specifically compare the CT techniques with these other imaging

studies on a segment by segment basis. It is well known that ECG and nuclear imaging (SPECT) have limited diagnostic accuracy for detection of myocardial infarction with generally low sensitivity (22% for ECG and 67% for SPECT) although high specificity for detection of myocardial infarction when compared to CMR as the reference standard{Andrade, 2009}, particularly for small infarctions. Similarly, regional wall motion abnormalities on echocardiography are not always present in prior myocardial infarcts detected by CMR, which may be related to small scar regions, non-transmural scar, or limited sensitivity of echocardiography to detect minor wall motion abnormalities{Catalano, 2005}. In our cohort there were 18 subjects with available ECG's for interpretation, with 7 demonstrating no evidence for pathologic Q waves or other findings suggestive of myocardial infarction despite other correlative imaging evidence demonstrating myocardial infarction. Similarly, there were 6 echocardiographic studies that demonstrated no regional wall motion abnormalities or other findings suggestive of myocardial infarction despite other correlative evidence including coronary angiography demonstrating prior myocardial infarction. Since late phase CCTA imaging may provide information similar to late enhancement CMR, CCTA may provide additional diagnostic and prognostic information beyond that provided by ECG, echocardiography and SPECT imaging that may be important in the management of these patients. Future studies of head to head comparisons of CCTA with other imaging techniques for detection of prior myocardial infarction including safety assessments for development of contrast nephropathy and radiation exposure are warranted."

3. In response to reviewer 02458760:

(1) please add the p values for comparisons between low and high voltage acquisitions in the result section, Table 2 and Figures 3-5

We do have all the p-values for each of the comparisons between each diagnostic performance variable and reconstruction type available, but did not list the individual values in Table 2 due to the format of the table which does not lend itself easily to a display of the corresponding p-values, which would need to be displayed in a table on its own. Thus, we have chosen to display the most relevant variables in Figures 3-5 with the listed significant p-values. The p-values for Figures 3-5 were included in the figure legends, but some of the reference symbols were inadvertently left out of the actual figure. The figures have been redone to indicate the significant differences as noted in the figure legend. We have also included the relevant significant variables in the last paragraph of the results section.

(2) a sample size calculation is lacking

Upon initial analysis, the sample size of 24 patients was considered adequate since it provided 90% power at the two-sided 5% significance level to detect a 5 percentage point difference between reconstruction algorithms or between the two diagnostic tests based on perfusion score (test positive = definite vs. test positive = possible or definite for enhancement abnormalities) in terms of accuracy for the detection of infarct segments and allowed diagnostic accuracy for each combination of algorithm and diagnostic test to be estimated with a precision no worse than 7 percentage points, where precision is the half-width of the 95% confidence interval. We have included this information in the revised manuscript.

(3) Please report medications in Table 1

Unfortunately, other than medications used as part of the CT scan portion of the study, other medications that the patient was taking was not routinely recorded as part of this study. We have now updated Table 1 to included the medications used as part of the CT acquisition.

4. In response to reviewer 02468825:

(1) The title: please identify the article as a study of diagnostic accuracy

We have shortened and reworded the title to: "Diagnostic Accuracy of Cardiac Computed Tomography Angiography for Myocardial Infarction" as suggested by the reviewer and in order to comply with the

formatting text requirements of the journal.

(2) In the third universal definition of MI (2012), MI was classified as acute MI and prior MI. So I suggest use the term Prior MI instead of chronic MI

We have changed the term "chronic" to "prior" throughout the manuscript.

(3) About the reference standard: "Segments graded as hypokinetic, akinetic or dyskinetic were considered abnormal and classified as infarct segments..." This definition of infarct segment may be confounding since several other conditions can cause abnormal wall motion, such as bundle branch block. The definition of infarct segments should be "imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract" (Thygesen K, Circulation. 2012 Oct 16;126(16):2020-35).

We agree with this reviewer that conditions such as bundle branch block or prior cardiac surgery may demonstrate an abnormal septal wall motion that may confound our definition of infarct. However, we attempted to exclude these types of abnormal wall motion patterns by evaluating wall thickening in addition to wall motion for the overall contraction pattern. We have attempted to explain this better and have reworded this section also to conform better with the universal guidelines as recommended. This section now reads: "Segments were graded as normal, hypokinetic, akinetic or dyskinetic based on qualitative evaluation of wall thickening and motion (contraction pattern). Segments graded as hypokinetic, akinetic or dyskinetic with significant wall thinning that were deemed unrelated to abnormal conduction or prior cardiac surgery were considered abnormal and classified as infarct segments."

(4) "Datasets were evaluated in a random order in consensus by two experienced cardiac readers..." Interobserver variability in the interpretation of data should be reported (recommend using kappa statistic including 95% confidence intervals).

Since the datasets were evaluated in consensus, we did not have individual readers evaluate for myocardial hyperenhancement for all the studies. However, we did perform individual assessments for 7 randomly chosen subjects which included 433 interpretable segments. The kappa value for interobserver variability was good at 0.60±0.11. This data is now included in the results section.

(5) The following question should be discussed in the Discussion section. What is the advantage of current method compared with ECHO, since ECHO is a non-invasive, radio-free, and convenient method to identify infarct segments. The safety of index test, including contrast induced nephropathy and radiation exposure.

We agree that a comparison of CCTA with alternative techniques such as ECHO to identify prior MI would be interesting and provide additional clinical utility for this technique. However, given that at present there are many different CT technical algorithms for assessment of myocardial infarction,, leading to different contrast and radiation dosing amounts, the intent of this study was to evaluate different late phase CT imaging techniques to identify the most reliable CCTA technique for identification of myocardial fibrosis. Although we did have corroborating data with regard to infarct location using other imaging techniques, again, as this was not the focus of this study, we did not have a significant number of a single other technique to allow for statistically valid comparisons. This study serves as a preliminary step for a clinical study to compare CCTA with other imaging techniques in the assessment of myocardial fibrosis from prior MI and/or other non-ischemic etiologies. We have included a paragraph in the Discussion section to discuss our limited findings with what is known in the literature regarding diagnostic accuracy of different imaging modalities for detection of myocardial infarction. Please refer to above response 2-1 for additional details.

5. In response to reviewer 00060494:

(1) In your paper, how do you define the enrolled patients with old MI? By coronary study? or just by Hx of electronic records? In the results, it showed that not all patients had a definite CAD diagnosis

by coronary angiography. Under this situation, how can you show the statistical data? What is your standard data in comparison with the CCTA?

Prior MI was initially identified by patient's clinical history and then confirmed according to the universal definition of prior MI either by the presence of pathological Q waves on the ECG, imaging evidence of a region of loss of viabble myocardium that is thinned and fails to contract or pathology findings of a prior MI present at surgery. This information was obtained by review of the patient's electronic medical record. Thus, although not all of the patients had coronary angiography available, we were still able to confirm the diagnosis of prior MI. We have revised the wording in the Materials and Methods (Study Population) section to clarify this.

(2) There are many easier tools to evaluate and confirm the patient with old MI, eg: EKG, echo and cardiac nuclear medicine. It is not deniable that this paper has its academic value but is less useful in clinical applications. Can you give more benefits of CCTA to confirm old MI than other methods in the conclusion section to the readers?

We agree that a comparison of CCTA with alternative techniques to identify prior MI would likely provide more clinical utility. However, given that at present there are many different CT technical algorithms for assessment of myocardial infarction, the intent of this study was to evaluate different late phase CT imaging techniques to identify the most reliable CCTA technique for identification of myocardial fibrosis. Although we did have corroborating data with regard to infarct location using other imaging techniques, again, this was not the focus of this study as we did not have a significant number of a single other technique to allow for statistically valid comparisons. This study serves as a preliminary step for a clinical study to compare CCTA with other imaging techniques in the assessment of myocardial fibrosis from prior MI and/or other non-ischemic etiologies. Please refer to response 2-1 above for additional details.

6. References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Radiology*.

Sincerely yours,

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